REMARKS

Claims 4-6, 11-14 and 16-31 are pending. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed July 26, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. §101 – Utility

The PTO rejects Claims 4-6, 11-14 and 16-31 as allegedly not supported by a specific and substantial asserted utility or a well established utility. The Examiner argues that since the function of the PRO1302 polypeptide has not yet been identified, the asserted utility is not substantial.

The PTO points to three journal articles as demonstrating that what is often seen as a lack of correlation between mRNA levels and increased levels, that polypeptide levels cannot be accurately predicted from mRNA levels, and that there is no correlation with a known role in disease for genes less with less than 5-fold change in expression.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101 if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather,

any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to

> convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed nucleic acids have utility as diagnostic tools for cancer, particularly esophageal tumor. Applicants are not asserting that the claimed nucleic acids necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of esophageal cancer. Applicants' asserted utility rests on the following argument:

1. Applicants submit they have provided reliable evidence that PRO1302 mRNA is expressed at least two-fold higher in normal esophagus tissue compared to esophageal tumor tissue, and therefore the claimed nucleic acids are useful as diagnostic tools.

2. It is not necessary to know what role the PRO1302 gene plays in cancer to use its differential expression as a diagnostic tool.

3. Further, it is not required to prove that the PRO1302 polypeptide is also differentially expressed in esophageal tumor to establish the utility of the claimed nucleic acids.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO cites Hu *et al.*, Pennica *et al.* and Haynes *et al.* as teaching that transcript expression levels displaying a 5-fold change or less in tumor compared to normal did not evidence a correlation between altered gene expression and a known role in disease, and that polypeptide levels cannot be accurately predicted from mRNA levels;

2. The PTO asserts that since the specification does not disclose any specific function of the PRO1302 polypeptide, the claimed subject matter lacks substantial utility.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The PTO has not offered *any* evidence to support its argument that there is a lack of utility. The PTO's arguments in large part rest on the activity of the PRO1302 polypeptide, which is irrelevant to the pending claims.

First, the PTO has failed to offer any evidence to support a rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that the Haynes *et al.*, Pennica *et al.* and Hu *et al.* references are not contrary to Applicants' arguments, and therefore are not evidence to support the rejection for lack of utility. Third, Applicants submit that it is not necessary for the specification to teach the function of the PRO1302 gene or polypeptide in order for the claimed subject matter to have utility. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence

need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1302 Polypeptide is Differentially Expressed in Esophageal Cancer compared to Normal Tissue

Applicants submit that the experimental evidence provided in Example 18 and supported by the previously submitted declarations demonstrate that the mRNA encoding the PRO1302 polypeptide is differentially expressed in esophageal tumor relative to normal esophagus.

Regarding the gene expression data in the specification, Example 18 shows that the mRNA associated with protein PRO1302 was more highly expressed in normal esophagus compared to esophageal tumor tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1302 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold

difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1302 cDNA between esophageal tumor tissue and normal esophagus. Therefore, it follows

that expression levels of the PRO1302 gene can be used to distinguish esophageal tumor tissue from normal esophagus.

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) as teaching that transcript expression levels displaying a 5-fold change or less in tumor compared to normal did not evidence a correlation between altered gene expression and a known role in disease.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not less-prevalent ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less

differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Applicants submit that a lack of known role for PRO1302 in cancer does not prevent the use of the gene as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1302 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.*, U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No. 6,162,604 submitted as Exhibits 1-3 in the response filed May 13, 2005), even though they may or may not cause the disease itself. Similarly, the present

nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1302 cDNA between esophageal tumor and normal esophageal tissue. Therefore, it follows that expression levels of the PRO1302 gene can be used to distinguish esophageal tumor tissue from normal esophageal tissue. The PTO has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed nucleic acids as diagnostic tools for cancer, particularly esophageal tumors.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Because the claims are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression is not presently at issue. However, Applicants submit that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1302 polypeptide in tumor of the esophagus, it is more likely than not that the PRO1302 polypeptide is also differentially expressed.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted as Exhibit 5 in the Response mailed May 13, 2005) and (4th ed. 2002) (submitted as Exhibit 6 in the Response mailed May 13, 2005)). Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted as Exhibit 7 in the Response mailed May 13, 2005) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted as Exhibit 8 in the Response mailed May 13, 2005. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Zhigang at 4. Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted as Exhibit 9 in the Response mailed May 13, 2005, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The PTO states that polypeptide levels cannot be accurately predicted from mRNA levels levels, citing Pennica *et al.* and Haynes *et al.* for support.

The PTO cites Pennica *et al.* as teaching "a *lack* of correlation between mRNA levels and increased peptide levels." Office Action at 4, emphasis in original. However, in contrast to the PTO's characterization of the reference, Pennica teaches nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. Since Pennica provides no data whatsoever regarding protein expression, nothing in Pennica can support the assertion that there is a lack of correlation between mRNA levels and increased peptide levels. Accordingly, nothing in Pennica is contrary to Applicants' assertion that it is established in the art that changes in the level of mRNA are correlated to the changes in the level of protein.

The PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)) as support for the assertion that "polypeptide levels cannot be accurately predicted from mRNA levels." Office Action at 4. Because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in gene expression and changes in protein expression are not presently at issue. Thus, the Haynes reference is not relevant. However, even if this issue were important for the utility of the claimed nucleic acids, Haynes does not support the PTO's position.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented as Exhibit 2 in the response mailed June 6, 2005 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

And even if Haynes supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1302 mRNA is more highly expressed in normal esophageal tissue than in esophageal tumor, the PRO1302 polypeptide will also be more highly expressed in normal esophageal tissue than in esophageal tumor.

It is not necessary to establish the Function of the claimed nucleic acids in order to establish their Utility

The PTO concludes that the claimed nucleic acids lack utility by stating:

> Applicants do not know the function of the PRO1302 polypeptide. For this reason, detecting the PRO1302 mRNA or polypeptide has no specific function, since it is not useful to detect a protein for which a function has not yet been identified, and additionally might only be overexpressed in one normal tissue. Since the asserted utility for the PRO1302 polypeptide is not in currently available form, the asserted utility is not substantial. (Office Action at 7).

Thus, the PTO appears to base its holding that the claimed nucleic acids lack utility on the assertion that Applicants have not disclosed the function of the PRO1302 gene or polypeptide.

Applicants submit that a lack of known function for PRO1302 does not prevent its use as a diagnostic tool for cancer. Whether or not there is a known function of the PRO1302 gene or polypeptide is irrelevant to whether its differential expression can be used to assist in diagnosis

of cancer – one does not need to know why the PRO1302 gene is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact, the PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No.6,162,604 submitted as Exhibits 1-3 in the Response mailed May 13, 2005), even though they may or may not cause the disease itself. Similarly, the present nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that the PRO1302 mRNA is more highly expressed in normal esophagus compared to esophageal tumor. This assertion does not appear to be questioned by the PTO. This differential expression of PRO1302 mRNA suffices to make the claimed nucleic acids useful as diagnostic tools for cancer; there is no requirement that the function of the PRO1302 gene or polypeptide must be demonstrated in order to establish its utility.

The References cited by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In*

re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

No evidence of record casts any doubt on the Applicants' asserted utility. As stated above, the cited references are not sufficient to satisfy the PTO's burden of offering evidence that a person of skill in the art would have a reasonable doubt that a gene differentially expressed in certain tumors can be used as a diagnostic tool since the references do not address this issue. Given the lack of support for the PTO's position, and the supporting evidence provided by the Applicants for their position, one of skill in the art would be more likely than not to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly esophageal tumors.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1268 gene in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that that the gene for the PRO1302 polypeptide is expressed at least two-fold higher in normal esophagus than in esophageal tumor. These data are strong evidence that the PRO1302 gene is associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1302 gene with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly esophageal tumor, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted the following arguments to support its conclusion that the claimed invention lacks utility: (1) the PTO cites Pennica *et al.*, Haynes *et al.* and Hu *et al.* as teaching that transcript expression levels displaying a 5-fold change or less in tumor compared to normal did not evidence a correlation between altered gene expression and a known role in disease, and that polypeptide levels cannot be accurately predicted from mRNA levels; and (2) the PTO states that since the specification does not disclose any specific function of the PRO1302 mRNA or polypeptide, the claims subject matter lacks substantial utility. The PTO states that further research needs to be done to support the utility of the claimed nucleic acids. Applicants have addressed both arguments in turn.

First, Applicants have provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration. Therefore, Applicants have established a basis for the use of the claimed nucleic acids as diagnostic tools, particularly for esophageal cancer.

Second, Applicants have shown that since the claimed nucleic acids are useful for cancer diagnosis, it is not necessary to demonstrate the function of the PRO1302 gene or polypeptide in order to establish the utility of the claimed nucleic acids.

Third, Applicants state that whether the encoded polypeptide is also differentially expressed in certain tumors is currently not at issue in this application.

Applicants have shown that the Pennica *et al.* reference is irrelevant to the utility of the claimed nucleic acids. Applicants have also shown that the Hu *et al.* and Haynes *et al.* references are not contrary to Applicants' asserted utility. Taken together, these references do not satisfy the PTO's burden of offering evidence to prove that one of skill in the art would reasonably doubt the asserted utility.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the PRO1302 gene is differentially expressed in esophageal tumor compared to normal esophagus. This is not a general utility that would apply to the broad class of nucleic acids.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic tool. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids as diagnostic tools as set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 4-6, 11-14 and 16-31 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a

specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO rejects Claims 4-6, 11-14 and 16-31 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The PTO asserts the Applicants were not in possession of all or a significant number of polynucleotides that have 95-99% homology to SEQ ID NO:85, while retaining the function of SEQ ID NO:85.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the

invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:85, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:85, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203230, with the functional recitation as amended: "wherein said isolated nucleic acid is more highly expressed in normal esophagus compared to esophageal tumor" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO:85" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:85, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:85, the full-length coding sequence of the cDNA deposited under ATCC accession number 203230, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they

hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO:85, such that they hybridize to SEQ ID NO:85 or the related sequences under the specified high stringency conditions recited in the claims.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:85 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in normal esophagus compared to esophageal tumor" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must

share the same expression pattern in esophageal tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in esophageal tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

The PTO has responded to these arguments by stating that "even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1302 polynuceotides" and that "Applicants made no variant polynucleotides." Office Action at 8.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***
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> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the Applicants in *Wallach* to actually make and individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could "envision the

detailed chemical structure of all or a significant number" of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:85, and claim polynucleotides which are homologous to it and have the functional limitation of differential expression. It is routine in the art to create polynucleotides which have at least 95% or 99% sequence identity to SEQ ID NO:85 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which polynucloetides share the requisite expression patterns. These structure/function combinations are sufficient to describe the claimed polynucleotides. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus to adequately describe the genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:85, by specifying the high stringency conditions under which hybridization occurs, and by describing the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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